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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,793	05/30/2001	Stephen Joseph Vesper	VESPER1	5682

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,793	VESPER, STEPHEN JOSEPH	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-24-04 has been entered.

The amendment filed 2-24-04 has been entered into the record. Claims 1-22 have been cancelled. Claims 23-33 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

The rejection of claims 3-5 and 19-21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn because the issues therein are not applicable to the newly submitted claims.

Rejections Maintained

Claims 23 and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakaguchi et al (Japanese Journal of Medical Mycology, 25(3):Abstract, 1984) in view of Harlow et al (Antibodies A Laboratory Manual, Cold Spring Harbor Press, 1989, pages 390-393) is maintained for reasons made of record for claims 2-3 and 19-21 in the final rejection of 12/19/2003.

The claims are drawn to a method for determining if an animal has been exposed to a hemolysin-producing fungus comprising contacting a sample from the mammal with labeled antibodies that bind to hemolysin produced by the fungus and detecting any complex formed by the labeled antibodies and the hemolysin.

Sakaguchi et al teach the immunohistochemical detection of the secretion of Asp-hemolysin in tissues (i.e. the instant sample) from a mouse infected with *Aspergillus fumigatus* (i.e. the instant mammal). Sakaguchi et al specifically teach "An attempt was made to detect the fungi and the production of hemolysis in various tissues during the infection. Toxins dyed blue were actually detected in the kidneys and brain. In mice inoculated with 10^7 spores via the coccygeal vein, the production and secretion of toxins were detected after two days on the periphery of the fungi in the renal cortex and cerebrum. In mice still alive two weeks after inoculation with 5×10^6 spores, the presence of toxins dyed blue on the periphery of fungi was confirmed in the glomerular tissue and some urinary tubes of the kidneys (Fig. 2). These results were similar to the ones reported by Iwada et al.11 indicating that the growth of *A. fumigatus* was most prevalent in the kidneys and brain in experimental fungal infections.

Using the indirect immunoenzymatic method, the production and secretion of hemolysin were actually confirmed in an infected organism." The immunohistochemical method uses and indirect enzyme labeled peroxidase binding IgG antibody (see English Abstract). The method differs by labeling the second or indirect antibody, rather than the primary or binding antibody.

Harlow et al teaches that in immunohistochemical techniques the antibodies can be labeled directly. Harlow et al teach that both the direct and indirect methods are in common use and that the labeling of the primary or binding antibody provides for the advantage of cleaner signals with lower background (see page 390, first full paragraph). Further, Harlow et al teaches that the labeled primary antibodies may be labeled with enzymes, fluorochromes or iodine (see page 392, section 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time that the invention was made to modify the immunohistochemical assay for the detection of Asp-hemolysin in a mammalian sample because Harlow et al teaches that labeled primary antibody provides for the advantage of cleaner signals with lower

background and that both the direct and indirect methods are in common usage. It would have also been *prima facie* obvious to substitute the enzyme label in the method as combined supra for any other appropriate label according to Harlow et al (fluorochromes or iodine) to label the primary antibody for detection of the Asp-hemolysin because Harlow et al teach that these are conventional alternative labels for a labeled primary antibody for histochemistry.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that Sakaguchi et al doe not teach or suggest that one can detect a specific fungus by using antibody to the hemolysin produced by that fungus. This is not persuasive, Sakaguchi et al specifically teach using the indirect immunoenzymatic method, the production and secretion of hemolysin were actually confirmed in an infected organism. As such, hemolysin is a marker for the hemolysin-producing fungus *Aspergillus fumigatus*. The method as combined practices the methods steps as claimed. As such, the method as combined detects the specific *Aspergillus fumigatus* hemolysin. Applicants argue that the art does not teach that hemolysin is species-specific. The claim does not require species specificity as asserted, merely exposure to a specific hemolysin producing fungus.

New Objections/Rejections Based on Amendment

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification fails to provide written description support for the new term "specific hemolysin-producing fungus". Applicants are specifically cautioned against adding new matter to the specification to support the now claimed invention.

Claim 33 is rejected under 35 U.S.C. 102(b) as being anticipated by Sakaguchi et al (Japanese Journal of Medical Mycology, 25(3):Abstract, 1984).

The claim is drawn to a method for determining if an animal has been exposed to a specific hemolysin-producing fungus comprising detecting the presence of the hemolysin produced by the fungus in a sample from the animal, the presence of the hemolysin in the sample indicating that the animal has been exposed to the hemolysin producing fungus.

Sakaguchi et al teach the immunohistochemical detection of the secretion of Asp-hemolysin in tissues (i.e. the instant sample) from a mouse (i.e. the instant animal) infected with hemolysin producing *Aspergillus fumigatus* (i.e. the instant hemolysin-producing fungus). The immunohistochemical method uses and indirect enzyme labeled peroxidase binding IgG antibody. Sakaguchi et al specifically teach "An attempt was made to detect the fungi and the production of hemolysis in various tissues during the infection. Toxins dyed blue were actually detected in the kidneys and brain. In mice inoculated with 10^7 spores via the coccygeal vein, the production and secretion of toxins were detected after two days on the periphery of the fungi in the renal cortex and cerebrum. In mice still alive two weeks after inoculation with 5×10^6 spores, the presence of toxins dyed blue on the periphery of fungi was confirmed in the glomerular tissue and some urinary tubes of the kidneys (Fig. 2). These results were similar to the ones reported by Iwada et al.11 indicating that the growth of A. fumigatus was most prevalent in the kidneys and brain in experimental fungal infections.

Using the indirect immunoenzymatic method, the production and secretion of hemolysin were actually confirmed in an infected organism."

As such, the method of Sakaguchi et al determines if the animal has been exposed to hemolysin-producing fungus by detection of the hemolysin in renal cortex and cerebrum of mice (i.e. the instant animal). Sakaguchi et al teach that the production and secretion of hemolysin were actually confirmed in an infected organism (mouse). As such, Sakaguchi et al anticipates the instantly claimed invention because it determines infection by

detection and secretion of hemolysin from the hemolysin-producing fungus *Aspergillus fumigatus*. The mice were exposed to the hemolysin producing fungus *Aspergillus fumigatus* and the exposure was detected by detection of hemolysin in samples from the mice. Sakaguchi et al inherently anticipate the claimed invention. Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999). The mouse was exposed to a hemolysin-producing fungus and the hemolysin was detected in tissues using an immunohistochemical method. As such, the presence of hemolysin in the tissue sample is a *de facto* marker of exposure to *Aspergillus fumigatus* hemolysin.

Claims 23-29 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants argue that the limitation of "a specific hemolysin-producing fungus" is meant and intended to be read as "species specific". First, the specification lacks basis for claiming "a specific hemolysin-producing fungus" and Applicant has not pointed to the specification by page and line number where written description support for this claim language can be found. Further, the there is no conception or written description of any hemolysin being species-specific. The species-specificity of hemolysins is not discussed in the specification, there is no comparison of hemolysins of different Fugal genera, much less any discussion of different species within the same genera nor the ability of any antibody to discriminate between them. The specification fails to provide written description support for the phrase "specific hemolysin-producing fungus" and clearly fails to provide for conception of using hemolysins to distinguish different species within the same genera as argued. This issue is best resolved by Applicants pointing to the

specification by page and line number where written description support can be found for the specific language and the asserted interpretation of such can be found.

Claims 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are drawn to a method for determining if a building contains a hemolysin-producing fungus comprising, obtaining a sample from the building, contacting the sample with labeled antibodies and detecting any complex formed between the labeled antibodies and the fungal hemolysin or active fragments of the hemolysin. The specification at paragraphs [0018] and [0036] teach screening of buildings for hemolysin-producing fungi. In these passages, a strain of fungus is obtained from the building is grown in a synthetic medium at a suitable incubation temperature and a culture filtrate is applied to a 5% sheep blood agar plate. If the filtrate is shown to be hemolytic, the strain is problematic and may pose a health risk. These passages of the specification do not provide for the concept of contacting a building sample with a labeled antibody to detect the hemolysin. This issue is best resolved by Applicants specifically pointing to the passage in the specification where the now claimed method has written description support. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Claims 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for determining if a building contains a hemolysin-producing fungus comprising, obtaining a sample from the building, contacting the sample with labeled antibodies and detecting any complex formed between the labeled antibodies and the fungal hemolysin or active fragments of the hemolysin. The specification at paragraph [0025] indicates that growing *S. chartarum* in trytpic soy broth in an incubator at 36±1° provides for a culture supernatant comprising fungal hemolysin. The specification fails to teach that the fungal hemolysin is present on the outside of spores or conidia as are conventionally found in buildings, such that a labeled antibody would bind. The presence of detectable hemolysin in a non-cultured environmental sample has not been tested nor contemplated by the specification. The specification fails to teach that the hemolysin is directly detectable in an environmental sample. There is no evidence in the art of any fungal spore or conidia having detectable hemolysin on its surface. While the art teaches detection of bacterial spores using spore-specific antibodies and particular immunological methods, this specification does not teach that the hemolysin is readily available on the spore or conidia coat. The specification fails to teach that the presence of fungal-hemolysin can be detected in a crude building sample in the absence of broth culture. As such, one skilled in the art would have to determine if the hemolysin was present on the surface of the fungal spores or conidia before any assessment of the presence or absence in a building sample could begin. Further, even if the spore surface had the hemolysin present. it is unclear if the method as claim is sensitive enough to detect the levels present in a crude building sample. Even the specification teaches that a strain must be isolated, liquid cultured and the culture supernatant tested on sheep blood agar. The courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* (CCPA) 153 USPQ 48). In the absence of further guidance by

Applicants, the specification as filed fails to enable the detection of a hemolysin-producing fungus by the claimed method.

Status of Claims

Claims 23-33 stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-F 6:30 am - 3:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patricia A. Duffy

Primary Examiner

Art Unit 1645